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July 15, 2003

Dr. William Freas
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Yuan-Yuan Chiu, Ph.D.
Office of New Drug Chemistry
Food and Drug Administration
5600 Fishers Lane, Room 13B31
Rockville, MD 20857

Re: TSE Advisory Committee

Dear Drs. Freas and Chiu:

We write on behalf of our clients, the Gelatin Manufacturers of Europe (GME) and the Gelatin Manufacturers Institute of America (GMIA). As you know, leaders of GME and GMIA will make presentations on July 17, 2003, to FDA's TSE Advisory Committee. At this time, we have had an opportunity to review the planned "Questions to the Committee" prepared by the agency concerning the "Safety of bovine bone gelatin in oral and topical drugs, food and cosmetics" as made available on FDA's website. (Copy attached.)

GME and GMIA respectfully request that the Questions to the Committee be somewhat revised to help improve their accuracy and completeness. Our specific requests are as follows:

1. Question 1 currently reads, "Do the results of these new studies demonstrate a reduction in infectivity that is sufficient to protect human health?" In practice, the safety of gelatin is based on two principles: (1) the use of healthy raw materials (in Europe, this involves controls on raw materials imposed by the European Union and by GME member companies), and (2) the use of manufacturing processes that can eliminate any potential infectivity that might theoretically be present in raw materials (in Europe, this involves the use of manufacturing processes that have been audited by FDA and that have been demonstrated by GME's studies to significantly reduce infectivity). Accordingly, to improve the accuracy and completeness of Question 1, we request that this question be revised to read:

> "Based on the use of raw materials sources and gelatin manufacturing processes as described in the information presented to the Committee (and as previously

audited by FDA), do the results of these new studies demonstrate a reduction in infectivity that is sufficient to protect human health?"

2. Question 2.a. currently asks whether the scientific data and information available support the current FDA Guidance for Industry on bone gelatin, and question 2.b. states, "If the answer is NO, what specific changes does the Committee recommend? In response to question 2.b., the Committee might answer that the scientific data support modification of the Guidance so as to improve the opportunity for European raw materials to be brought into compliance with the guidance, while at the same time maintaining adequate controls on the use of European raw materials in the production of gelatin.

Recognizing that the Committee may take this approach, we request that the Committee be asked to address two potential modifications to FDA's Guidance that, if implemented, would improve the opportunity for European raw materials to be brought into compliance with the Guidance, while at the same time maintaining adequate controls on the use of European raw materials in the production of gelatin. These potential modifications are as follows:

a. FDA's Guidance currently requires that "cattle come from BSE-free herds." At this time, there is no uniform definition of a "BSE-free herd" and there is no means of determining whether a herd is BSE-free except by post-mortem testing. As a practical matter, this term refers to a herd in which there has not been a single animal identified with BSE. (This practical definition is consistent with a 1997 discussion of this term by the TSE Advisory Committee. Transcript of April 23, 1997 meeting, p. 49.) In Europe, generally accepted testing practices are that animals over 30 months of age are normally tested for BSE, whereas animals under that age are normally not tested because they have not been defined to pose a risk to human health. Thus, in practice, a "BSE-free herd" is a herd in which BSE has not been detected in tests of animals over 30 months of age. FDA's Guidance in this regard would be clearer if it were to include a brief explanation of the term "BSE-free herd," for example, by stating "BSE-free herd (as determined by generally accepted testing practices)."

b. FDA's Guidance currently requires that heads, spines and spinal cords be removed from gelatin raw materials "directly after slaughter" or "as the first procedure following slaughter." GME has previously outlined, in a letter to FDA of November 9, 1998 (copy enclosed), why the removal of spines (vertebrae) may be done at any time during the de-boning process (as was recommended by the Committee in 1998). (The removal of heads and spinal cords is not an issue because they are already normally removed at the time of slaughter.) It continues to be appropriate for FDA's Guidance to be modified to permit the removal of spines at any time during the de-boning process.

Accordingly, to improve the accuracy and completeness of Question 2.b., we request that this question be revised to read:

> "If the answer is NO, what specific changes does the Committee recommend? If the Committee recommends that the scientific data support modification of the Guidance so as to improve the opportunity for European raw materials to be brought into compliance with the guidance, while at the same time maintaining adequate controls on the use of European raw materials in the production of gelatin, does the Committee support the following changes in the language of FDA's recommendations: (1) including a brief explanation of the term 'BSE-free herd,' by stating 'BSE-free herd (as determined by generally accepted testing practices);' and (2) revising the requirement that the slaughterhouse remove spines (vertebrae) directly after slaughter to provide for such removal at any time during the de-boning process, (as was recommended by this Committee in 1998)? If these changes were made, Recommendation 4 of the Guidance would read as follows:
>
> At this time, there does not appear to be a basis for objection to the use of gelatin in FDA-regulated products for oral consumption and cosmetic use by humans when the gelatin is produced from bones obtained from cattle residing in, or originating from, BSE countries, if the cattle come from BSE-free herds (as determined by generally accepted testing practices) and if ~~the slaughterhouse removes the heads, spines and spinal cords directly after slaughter~~ heads, spines and spinal cords are removed. Nor does there appear to be a basis for objection to gelatin for oral consumption and cosmetic use which is produced from bones from countries which have not reported BSE but which fail to meet OIE standards if ~~the slaughterhouse removes the heads, spines and spinal cords directly after slaughter~~ heads, spines and spinal cords are removed. ~~Gelatin processors should ensure that slaughterhouses that supply bovine bones for gelatin production remove heads, spines and spinal cords as the first procedure following slaughter~~.

In raising the issues outlined above, it is our intent to assist FDA in formulating questions for the committee that are as accurate and complete as possible. If FDA elects not to raise these issues with the Committee, GME and GMIA would like to discuss these issues briefly (approximately 5 to 10 minutes) during the public session of the meeting. Of course, we wish to

do so in a manner fully cooperative with FDA, and we would ask that you let us know of any questions or comments you may have in this regard.

Thank you for your kind consideration of these requests.

Sincerely,

David A. Bieging
Dorsey & Whitney LLP
Counsel to GMIA

Daniel R. Dwyer
Kleinfeld, Kaplan & Becker
Counsel to GME

Attachments

Safety of bovine bone gelatin in oral and topic drugs, food and cosmetics

GME/GMIA proposed modified questions to the committee

1. "Based on the use of raw materials sources and gelatin manufacturing processes as described in the information presented to the Committee (and as previously audited by FDA), do the results of these new studies demonstrate a reduction in infectivity that is sufficient to protect human health?"

2a. Do the scientific data and information available support the following current FDA recommendation on bone gelatin

"At this time, there does not appear to be a basis for objection to the use of gelatin in FDA-regulated products for oral consumption and cosmetic use by humans when the gelatin is produced from bones obtained from cattle residing in, or originating from, BSE countries, if the cattle come from BSE-free herds and if the slaughterhouse removes the heads, spines, and spinal cords directly after slaughter. Nor does there appear to be a basis for objection to gelatin for oral consumption and cosmetic use which is produced from bones from countries which have not reported BSE but which fail to meet OIE standards, if the slaughterhouse removes the heads, spine, and spinal cords after slaughter. Gelatin processors should ensure that slaughterhouses that supply bovine bones for gelatin production remove heads, spines, and spinal cords as the first procedure following slaughter"?

2b. If the answer is NO, what specific changes does the Committee recommend?

If the Committee recommends that the scientific data support modification of the Guidance so as to improve the opportunity for European raw materials to be brought into compliance with the guidance, while at the same time maintaining adequate controls on the use of European raw materials in the production of gelatin, does the Committee support the following changes in the language of FDA's recommendations: (1) including a brief explanation of the term 'BSE-free herd,' by stating 'BSE-free herd (as determined by generally accepted testing practices);' and (2) revising the requirement that the slaughterhouse remove spines (vertebrae) directly after slaughter to provide for such removal at any time during the de-boning process, (as was recommended by this Committee in 1998)? If these changes were made, Recommendation 4 of the Guidance would read as follows:

> At this time, there does not appear to be a basis for objection to the use of gelatin in FDA-regulated products for oral consumption and cosmetic use by humans when the gelatin is produced from bones obtained from cattle residing in, or originating from, BSE countries, if the cattle come from BSE-free herds (as determined by generally accepted testing practices) and if ~~the slaughterhouse removes the heads, spines and spinal cords directly after slaughter~~ heads, spines and spinal cords are removed. Nor does there appear to be a basis for objection to

gelatin for oral consumption and cosmetic use which is produced from bones from countries which have not reported BSE but which fail to meet OIE standards if ~~the slaughterhouse removes the heads, spines and spinal cords directly after slaughter~~ heads, spines and spinal cords are removed. ~~Gelatin processors should ensure that slaughterhouses that supply bovine bones for gelatin production remove heads, spines and spinal cords as the first procedure following slaughter.~~